prophylaxis must not be given to patients with active tuberculosis.

There is no evidence that rifabutin is effective as prophylaxis against *M tuberculosis.* Patients requiring prophylaxis against both *M tuberculosis* and *M avium-intracellulare* may be given isoniazid and rifabutin concurrently.

Problems with polypharmacy may arise with the prophylaxis and the treatment of multiple potential opportunistic infections; as a result of this therapy, however, HIV-infected patients can expect to increase not only the duration but the quality of their life.

Compassion, understanding, and a working knowledge of new and emerging treatment options are prerequisites for the optimal management of HIV disease, which should now be considered a chronic manageable condition.

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Treatment and Prevention of Milk Allergy

COW'S MILK ALLERGY is a notable clinical problem, affecting about 1% of all infants. The most clearly understood manifestations are immunoglobulin (Ig) E-mediated and include anaphylaxis, urticaria, eczema, rhinitis, and asthma. The mechanisms for milk-induced enterocolitis, the malabsorption syndrome, and colic are unknown. The major cow's milk proteins implicated in allergic disease are casein and the whey proteins, α-lactalbumin, β-lactoglobulin, bovine serum albumin, and bovine serum γ-globulin. β-Lactoglobulin is thought to be the most allergenic. The diagnosis of milk allergy is based on a careful history, the demonstration of IgE antibodies either by epicutaneous skin test or radioallergosorbent test, and elimination and challenge when this can be safely done. The gold standard, however, a double-blind, placebo-controlled challenge test, is used when the diagnosis is in doubt and is mandatory when a new hypoallergenic formula is being tried.

For more than 50 years, intact animal and vegetable proteins have been used as substitute nutritional sources in infants with milk allergy. Soy formulas, however, have been shown to provoke allergic reactions—although not usually anaphylaxis—in cow's milk-sensitive infants, and yet they continue to be considered hypoallergenic by the medical community.

Cow's milk hydrolysates have been used for more than 40 years, but only recently have they been studied carefully, since even these products have produced anaphylaxis in a highly allergic infant. Cow's milk hydrolysates are derived from casein (such as Nutramigen, Pregestimil, and Alimentum) or whey (such as Good Start and Alfare, which is not available in the United States). These preparations are produced by exposing intact cow's milk protein to proteolytic enzymes, heat, and ultrafiltration. Preclinical evaluation has included physiochemical and immunologic testing to determine their antigenicity. Allergenicity has been assessed by the guinea pig anaphylaxis model and such in vitro analyses as the enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay inhibition. For example, extensively hydrolyzed casein when analyzed by ELISA inhibition shows a decrease in allergenicity of more than 99%. The upper limits of tolerance are unknown, however, and may vary among infants.

Preclinical tests cannot predict with certainty that infants with cow's milk allergy will not react adversely to a hypoallergenic formula. Thus, labeling an infant formula as hypoallergenic requires careful clinical testing. It should be recognized that all formulas will produce reactions in some infants. All new hypoallergenic formulas must first be tested for their ability to promote normal growth and maintain a normal nutritional state. Thereafter, a double-blind, placebo-controlled challenge followed by an open challenge is required for formulas intended for infants with cow's milk allergy. The Committee on Nutrition of the American Academy of Pediatrics advises that for a formula to be labeled hypoallergenic, it should be tolerated by 90% of milk-allergic infants. The only formulas that currently have been shown to fulfill these criteria are Nutramigen, Pregestimil, and possibly Alimentum. These, therefore, are appropriate for use in a highly milk-sensitive infant.

Hypoallergenic does not mean nonallergenic, and, as indicated, anaphylaxis has been reported even with the formulas with known tolerance. To deal with this possibility, in this population it would be prudent to give the first dose in a setting where resuscitation can be initiated. Skin testing with these formulas might also prove helpful in this regard because a negative skin test is usually highly predictive, whereas a positive response is associated with a reaction in 30% to 40% of cases. Nonetheless, the proof is in the eating. Whether soy-based formulas would be useful in a highly milk-allergic infant is controversial at best. Faced with a highly milk-sensitive infant, most physicians recommend giving a casein hydrolysate at least for the first year and then reassessing the allergic status. A soy formula could be tried only if cost prohibits the use of a casein hydrolysate.

To prevent milk allergy, several studies have suggested that the mothers of these infants breast-feed and limit their intake of cow's milk; Nutramigen can be used as a supplement or alone. Recent studies also suggest that partially hydrolyzed preparations such as Good Start, but not soy-based formulas, may be effective as a preventive formula. These preventive measures should be continued for the first 6 to 12 months of life to be effective for children with a family history of food allergies.

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Exercise-Induced Asthma and Anaphylaxis

ALTHOUGH EXERCISE is a salutary activity for many people, for others it may provoke anaphylaxis or asthma. Exercise-induced asthma and exercise-induced anaphylaxis rarely occur in the same person and are thus considered separate disorders. The common factor is the form of exercise, which is almost invariably intense running for relatively short periods.

Exercise-induced asthma is defined as a transitory increase in airway resistance that follows vigorous exercise. It can be reproduced in the laboratory in about 80% of patients with asthma who exercise at 80% to 90% of their predicted maximal working capacity for six to eight minutes while breathing room air. The severity cannot be predicted by the resting level of lung function. Even persons with normal lung function can suffer severe asthma within minutes of completing exercise. Inhalation of a β-adrenergic aerosol or cromolyn sodium before exercise will prevent the occurrence in 90% of people with this reaction. The rest require either larger than usual doses or a combination of drugs for relief.

Proposed mechanisms for airway narrowing include the release of mast cell mediators such as histamine, the stimulation of vagal afferent pathways, and reactive local hyperemia and edema initiated not by an immunologic response but by abnormal water loss in the airways. Water loss results from a combination of temperature drop in the bronchial mucosa and hyperosmolarity of the periciliary fluid. Exercise-induced asthma has been prevented by having a patient inhale warmed or moist air during exercise.

Exercise-induced anaphylaxis can develop in persons without a history of asthma or even any allergic condition, although about half appear to be atopic. The prevalence is unknown, but one center has seen 500 cases over a 17-year period. Patients typically have a sensation of cutaneous warmth and pruritus initially, followed rapidly by generalized erythema, urticaria, hypotension, and upper respiratory tract obstruction during physical activity. Asthma rarely occurs. Although the reactions appear life-threatening and may require medical therapy for anaphylaxis, deaths have not been reported. Most patients are adolescents or younger adults, but the condition has been reported in a 4-year-old child.

Exercise-induced anaphylaxis may require another factor, food ingestion, with the physical activity. Anaphylaxis develops in some patients only in association with either a meal followed by exercise or eating a specific food for which they have immunoglobulin E antibodies. Strangely enough, either factor alone in this group with food-dependent, exercise-induced anaphylaxis will not provoke a generalized reaction. In addition, a familial tendency has been found in some cases.

A common mechanism has not been found for these diverse forms of exercise-induced anaphylaxis. A release of mediators such as histamine has occurred in only about half of the patients studied. Some with food dependency may have exaggerated blood volume shifts from the skeletal muscle circulation to the splanchnic vasculature during food digestion; others have demonstrable autonomic nervous system dysfunctions. Shared leukocyte antigen haplotypes have been found in the familial form.

Treatment may be defined as active or preventive. Active treatment is identical to the treatment of any type of anaphylaxis. Prevention involves restriction or changing the form of exercise and, in the food-dependent type, permitting exercise only before food intake. Pretreatment with histamine-1 antagonists or gradual increments of exercise has not proved uniformly effective. Exercise-induced asthma and anaphylaxis can be readily diagnosed and ameliorated by preventive meaures.

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Antihistamines and the Heart

THE TOXICITIES OF classic, first-generation histamine-1–receptor antagonist antihistamines have produced sedation, decreased mental alertness, and anticholinergic side effects. Beyond scattered reports of palpitations or hypotension in antihistamine overdosage, few serious adverse cardiovascular reactions have been described with the use of these agents.

With the development of second-generation, nonsedating H_1-receptor blockers, the spectrum of side effects has changed. Terfenadine, a relatively short-acting antihistamine that is extensively metabolized by the hepatic cytochrome P-450 system, induces a small increase in the corrected QT interval on electrocardiography, even at recommended dosages. This electrocardiographic change is rarely clinically important. When terfenadine is administered to patients with impaired hepatic function or given simultaneously with the macrolide antibiotics erythromycin or troleandomycin or with the imidazole antifungals ketoconazole or itraconazole, the QT interval may be more dramatically prolonged. This has resulted in serious ventricular tachyarrhythmias (including torsades de pointes and ventricular fibrillation) and death. These agents appear to alter terfenadine pharmacokinetics and may cause the accumulation of terfenadine in certain patients.